Cognitive Impairment in Cocaine Users is Drug-Induced but Partially Reversible: Evidence from a Longitudinal Study

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Cognitive impairment in cocaine users is drug-induced but partially reversible: evidence from a longitudinal study

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Abstract

Cocaine users consistently display cognitive impairments. However, it is still unknown whether these impairments are cocaine-induced and if they are reversible. Therefore, we examined the relation between changing intensity of cocaine use and the development of cognitive functioning within one year. The present data were collected as part of the longitudinal Zurich Cocaine Cognition Study ($ZuCo^2St$). Forty-eight psychostimulant-naïve controls and 57 cocaine users (19 with increased, 19 with decreased, and 19 with unchanged cocaine use) were eligible for analysis. At baseline and after a one-year follow-up, cognitive performance was measured by a global cognitive index and four neuropsychological domains (attention, working memory, declarative memory, executive functions), calculated from 13 parameters of a broad neuropsychological test battery. Intensity of cocaine use was objectively determined by quantitative six-month hair toxicology at both test sessions. Substantially increased cocaine use within one year (mean +297%) was associated with reduced cognitive performance primarily in working memory. By contrast, decreased cocaine use (-72%) was linked to small cognitive improvements in all four domains. Importantly, users who ceased taking cocaine seemed to recover completely, attaining a cognitive performance level similar to that of the control group. However, cognitive recovery was correlated with age of onset of cocaine use – early onset users showed hampered recovery. These longitudinal data suggest that cognitive impairment might be partially cocaine-induced but also reversible within one year, at least after moderate exposure. The reversibility indicates that neuroplastic adaptations underlie cognitive changes in cocaine users, which are potentially modifiable in psychotherapeutical or pharmacological interventions.

Keywords: Reversibility, stimulants, brain maturation, neuropsychology, cognition, cocaine

Introduction

The annual number of cocaine users is currently estimated at 17 million people worldwide (United Nations Office on Drugs and Crime, 2013). Because of its high addictive potential and harmful effects on mental and physical well-being (Degenhardt and Hall, 2012; Nutt *et al*, 2007), the use of cocaine is a major public health issue with substantial societal and economic costs (Degenhardt *et al*, 2012). Accumulating evidence suggests that dependent (Goldstein *et al*, 2004; Jovanovski *et al*, 2005; Vonmoos *et al*, 2013; Woicik *et al*, 2009) and also recreational (Colzato *et al*, 2009; Reske *et al*, 2010; Soar *et al*, 2012; Vonmoos *et al*, 2013) cocaine use is associated with broad neuropsychological impairment. Remarkably, a first study indicates that 30% of dependent users, and even 12% of recreational users exhibit clinically relevant global cognitive impairment (Vonmoos *et al*, 2013). Studies have shown deficits in attention, working memory, and declarative memory in chronic cocaine users, whereas the heterogeneous concept of executive functions has yielded mixed results (Jovanovski *et al*, 2005; Vonmoos *et al*, 2013). We recently demonstrated that cocaine users additionally display inferior social cognition, including prosodic and cross-modal emotion recognition, emotional empathy, mental perspective-taking, and social decision-making (Hulka *et al*, 2014; Hulka *et al*, 2013; Preller *et al*, 2013). A worse social cognitive performance was correlated with a smaller social network and more criminal offenses in cocaine users (Preller *et al*, 2013), pointing to the importance of cognitive health for social and occupational functioning in drug users as in psychiatric patients (Lee *et al*, 2013). Moreover, neuropsychological performance predicts the attainment of treatment objectives and the likelihood of treatment dropout in substance users (Teichner *et al*, 2002). Today, it is still unclear whether these cognitive impairments are cocaine-induced and if they are reversible. Studies on chronic cocaine self-administration in rhesus monkeys suggest that some alterations in attention, learning, and working memory might be cocaine-induced (Gould *et al*, 2012; Liu *et al*, 2008; Porter *et al*, 2011). In contrast to these animal studies, research with human cocaine users has focused on the effects of drug abstinence on cognition. The few and preliminary cross-sectional (Bolla *et al*, 1999; De Oliveira *et al*, 2009) and longitudinal (Bauer, 1996; Bolla *et al*, 2000; Di Sclafani *et al*, 2002; van Gorp *et al*, 1999) studies either indicate persisting neuropsychological impairment in attention (Bauer, 1996), declarative memory (van Gorp *et al*, 1999), and executive

function (De Oliveira *et al*, 2009), or suggest some recovery effects in working memory (Di Sclafani *et al*, 2002) and verbal declarative memory (De Oliveira *et al*, 2009). However, it should be noted that even longitudinal studies in humans cannot prove causal relationships between drug intake and cognition. Furthermore, cocaine use was self-reported and solely controlled with drug urine tests but not hair toxicology analyses, which would have enabled a reliable detection of drug use during the last months. Finally, these studies had relatively brief follow-up intervals with strongly varying abstinence durations (one week to six months) and several studies reported only minimal information on the severity of drug use. Notably, no longitudinal study has investigated the association between escalating cocaine use and cognitive impairment yet.

Accordingly, we aimed to overcome these limitations of previous studies by means of a longitudinal study specifically investigating the linkage between changing cocaine use and cognitive performance during a one-year interval. Therefore, we categorized cocaine users in the Zurich Cocaine Cognition Study (ZuCo^{2}St) as *decreasers*, *stable users*, or *increasers* after the one-year follow-up. We then compared the course of cognitive performance between *decreasers* and *increasers*, whose test scores were normalized to the test-retest effects of a psychostimulant-naïve control group that was also assessed twice. Because we were interested in the specific effects of cocaine, relatively pure users with little co-use of other illegal drugs were initially recruited. To objectively assess the initial severity and change in cocaine use and to control for co-use of other drugs, we performed quantitative hair and urine toxicology analyses at baseline and follow-up. Because we recently reported strong dose-response correlations between several cocaine use parameters and cognitive performance in cocaine users from the cross-sectional part of this study (Vonmoos *et al*, 2013), and based on previous animal studies suggesting that cognitive impairment in cocaine users might be drug-induced (Gould *et al*, 2012; Liu *et al*, 2008; Porter *et al*, 2011), we hypothesized that escalating cocaine use is associated with further cognitive impairment. Based on data suggesting that long-term cocaine abstinence of cocaine might be associated with partial recovery of neuropsychological performance (De Oliveira *et al*, 2009; Di Sclafani *et al*, 2002; van Gorp *et al*, 1999), we expect to find improved cognition in cocaine users with considerably decreased or ceased cocaine consumption.

Materials and Methods

Participants

From a cross-sectional sample of 234 participants, 48 psychostimulant-naïve controls and 57 cocaine users could be included in the longitudinal study (recruitment and selection details **Methods S1**). At baseline, general exclusion criteria were neurological disorders or head injuries, severe somatic diseases, and any medication affecting the central nervous system. Controls were also excluded if they displayed current or previous *DSM-IV* Axis I psychiatric disorders (except for nicotine addiction), and regular illegal drug use (>15 occasions lifetime, except for recreational cannabis use). Exclusion criteria for cocaine users were use of opioids, a polytoxic drug use pattern according to DSM-IV, and *DSM-IV* Axis I adult psychiatric disorders – except for cocaine, cannabis, nicotine, and alcohol abuse/dependence; history of affective disorders (current major depression was excluded); and attention deficit hyperactivity disorder (ADHD). Inclusion criteria for cocaine users were cocaine use of >0.5g per month, cocaine as primary drug, and an abstinence duration of <six months at baseline. Participants were asked to abstain from illegal substances for at least 72h and from alcohol for 24h before test sessions. Compliance with these instructions was controlled using urine screenings (semi-quantitative enzyme multiplied immunoassay method; for technical details see Vonmoos *et al*, 2013). Drug use severity was assessed by six-month hair toxicology analyses (liquid chromatography-tandem mass spectrometry; Vonmoos *et al*, 2013). The study was approved by the Cantonal Ethics Committee of Zurich. All participants provided written informed consent and received compensation for their participation.

Group assignment

The decisive criterion for replicable group assignment was a combination of absolute and relative changes in cocaine concentration in hair samples between baseline (t1) and follow-up (t2). The absolute criterion was based on a shift in cocaine concentration of at least ±0.5 ng/mg, according to a commonly accepted cut-off value for reliably detection of cocaine use (Bush, 2008; Cooper *et al*, 2012). The relative criterion was based on a minimal increase of 20% or a minimal decrease of 10% in the robust hair toxicology parameter $cocaine_{total}$ (=cocaine+benzoylecgonine+norcocaine)(Hoelzle *et*

al, 2008). According to these criteria, cocaine users were divided into three groups of similar size: 19 cocaine *increasers* consumed substantially more cocaine at follow-up (mean increase +30.4 ng/mg [+297%], range +0.5 to +268.5 ng/mg [+20% to +5374%], SD 61.9 ng/mg), whereas 19 cocaine *decreasers* consumed substantially less cocaine (mean decrease -10.6 ng/mg [-72%], range -116.9 to -0.6 ng/mg [-100% to -12%], SD 26.7 ng/mg), and 19 users with a relatively stable cocaine use pattern did not meet both criteria, and, thus, were not further analyzed (**Figure S1**).

Procedure

The test procedure was similar in baseline and follow-up. Trained psychologists conducted the Structured Clinical Interview for *DSM-IV* (SCID-I)(American Psychiatric Association, 1994). Drug use was assessed with a structured and standardized Interview for Psychotropic Drug Consumption (Quednow *et al*, 2004). Cognitive performance was assessed with a neuropsychological test battery comprising three tasks of the Cambridge Neuropsychological Test Automated Battery (CANTAB, www.cantab.com): Rapid Visual Processing (RVP), Spatial Working Memory (SWM), Paired Associates Learning (PAL); a German version of the Rey Auditory Verbal Learning Test (RAVLT)(Helmstaedter *et al*, 2001); and the Letter Number Sequencing Task (LNST)(Wechsler, 1997). At follow-up, parallel test-versions were used for the PAL, RAVLT, and LNST. In contrast to the cross-sectional analysis, we excluded the CANTAB Intra/Extradimensional Set Shifting (IED) from the longitudinal analysis because of an evident ceiling effect at baseline (Vonmoos *et al*, 2013). Analogous to the cross-sectional part of the study (Vonmoos *et al*, 2013), 13 predefined main cognitive test parameters were *z*-transformed on the basis of means and standard deviations of the control group (n=48) at baseline. If necessary, test scores were reversed so that high scores always indicated better cognitive performance. Test parameters were reduced to four cognitive domains (attention, working memory, declarative memory, and executive functions, for details see **Methods S2**). Furthermore, the four *z*-scored domains were equally integrated into a broad global cognitive index (GCI).

Statistical analysis

Statistical analyses were performed with SPSS Statistics 19.0 (IBM, Switzerland). Effect sizes were calculated in SPSS and with G*Power 3.1 (Faul *et al*, 2007). Frequency data were analyzed by means of Pearson's chi-square test. Group differences in cognitive test scores at baseline and follow-up were analyzed by analyses of variance (ANOVA). For the longitudinal analysis, cocaine user groups and subgroups were analyzed using mixed design analyses of covariance (ANCOVA), omnibus tests (group*time) were followed by Sidak-corrected pairwise pre-post comparisons adjusted for test-retest effects. Because ADHD has previously been linked to both, cognitive performance in cocaine users (Vonmoos *et al*, 2013) and substance use in general (Wilson, 2007), mixed design analyses were corrected for ADHD as measured by the ADHD Self-Rating scale (Roesler *et al*, 2004). Given that we expected inevitable test-retest effects in all groups and because we aimed to estimate the change of the cocaine using groups relative to the control group, in which the general cognitive performance should be constant across one year, we corrected the user groups' change scores by subtracting the mean change score of the control group. To relate cognitive change scores to varying cocaine use during the test interval, Pearson product-moment correlation analyses (two-tailed) were conducted in the cocaine user group. The confirmatory statistical comparisons were carried out on a significance level of $p<.05$ (two-tailed).

Results

Demographic characteristics and drug use

Controls, *increasers*, and *decreasers* did not differ regarding demographic data and time interval between baseline and follow-up (**Table 1,** for details considering the not further analyzed group of *stable* cocaine users, see **Table S1**). However, as previously shown, both cocaine user groups displayed significantly higher BDI and ADHD-self-report sum scores than controls (Vonmoos *et al*, 2013). Hair samples and cumulative doses revealed a clear dominance of cocaine compared with other illegal drugs, as intended by the inclusion and exclusion criteria. At baseline, *increasers* and *decreasers* displayed similar cocaine hair concentrations; however, at follow-up *increasers* showed an approximately 10-fold higher concentration of cocaine than *decreasers*. Whereas hair analyses for *increasers* showed a 3-fold increase between baseline and follow-up, *decreasers* displayed only a forth of the $cocaine_{total}$ hair concentration after one year. In contrast to baseline, none of the self-reported cocaine use parameters correlated with hair cocaine concentrations in the follow-up (r=.02-.29, p=.89-.08), highlighting the importance of objective drug use measures in longitudinal studies (**Table S2**).

Test scores at baseline

As previously demonstrated in the cross-sectional sample of this study (Vonmoos *et al*, 2013), ANOVAs showed significant group effects for the GCI, both memory domains, and the executive function but only a statistical trend for attention (**Table 2,** for details regarding single test parameters, see **Table S3**), indicating moderate to strong cognitive impairments in both cocaine user groups compared with controls (Cohen's d=0.47–0.79). *Increasers* and *decreasers* did not substantially differ in the GCI (p=.99, d=0.08) and all four domains ($p\geq$.94, $d\leq$0.14) at baseline.

Change between baseline and follow-up

Because of strong test-retest effects, at the follow-up all groups displayed a better performance on the GCI, all domains, and the majority of single tests compared to baseline (**Table 2**). Of note, test-retest improvements in controls and *decreasers* were substantially stronger than in the *increaser* group.

An ADHD-corrected mixed ANCOVA for the two user groups revealed a significant group*time interaction effect on working memory ($F_{1,35}$=4.85, p<.05, $_p\eta^2$=.12)(**Figure 1**). Furthermore, there was a non-significant trend for a group*time interaction in the GCI ($F_{1,35}$=2.96, p=.09, $_p\eta^2$=.08)(for a GCI analysis including the group of *stable* cocaine users, see **Figure S2**). However, the effect sizes of the group*time interactions regarding declarative memory ($F_{1,35}$=2.11, p=.16, $_p\eta^2$=.06), attention ($F_{1,35}$=.73, p=.40, $_p\eta^2$=.02), and executive functions ($F_{1,35}$=.15, p=.70, $_p\eta^2$=.004) were rather small.

In subsequent pairwise Sidak pre-post comparisons adjusted for test-retest effects (**Figure 1**, **Table S4**), *increasers* showed a significant cognitive decline in working memory (p<.05, d=-0.52). Additional exploratory analysis revealed small effect sizes for a decline in *increasers* with regard to declarative memory (d=-0.16), attention (d=-0.04), and GCI (d=-0.21). By contrast, performance improvements of the *decreasers* were not significant but revealed small to moderate effect sizes in attention (d=0.22), working memory (d=0.21), declarative memory (d=0.30), and the GCI (d=0.33).

Additionally, correlation analyses within a consolidated group of *increasers* and *decreasers* indicated a significant association between cumulative cocaine dose used during the test interval and change scores in attention (r=.34, p<.05) as well as a significant relation between changes in the hair parameter $cocaine_{total}$ and change scores in the declarative memory (r=.39, p<.05)(for details see **Table S5**).

As we have previously shown that age of onset was an important modulator of cognitive performance in cocaine users (Vonmoos *et al*, 2013), we further investigated whether age of onset was linked to the significantly different change in working memory of cocaine *increasers* and *decreasers* during the test interval. Whereas the *increasers* did not show any substantial correlation between age of onset and working memory change score (r=-.10, p=.68), there was a significant association in cocaine *decreasers* (r=.54, p<.05), indicating that early onset of cocaine use goes along with reduced recovery of working memory when cocaine use is considerably reduced (**Figure 2**).

To analyse whether *decreasers* recover depending on their initial level of cocaine use, we correlated their cocaine use levels at baseline (hair concentration $cocaine_{total}$) with the cognitive change scores. However, we did not find a significant correlation in the GCI (r=-.10, p=.68, n=19) or any other domain (r=-.35-.18, p=.14-.47, n=19).

Test scores at follow-up

In contrast to baseline, *decreasers* performed slightly, albeit non-significantly better than *increasers* on the GCI (d=0.37), all domains (d=0.14–0.42), and each single parameter (d=0.14–0.49)(**Table 2**). Accordingly, the domain differences between *decreasers* and controls were reduced to non-significant small to moderate effect sizes (d=0.24–0.59). Controls and *increasers* still differed significantly in the GCI (d=0.85), working memory (d=0.95), and declarative memory (d=0.78).

Impact of ceased and strongly intensified cocaine use

To investigate the impact of ceased or strongly intensified cocaine use, we split cocaine *increaser* (low/high; cut-off $\Delta_{t2\text{-}t1}$ $cocaine_{total}$=10 ng/mg), and *decreaser* subgroups (ceased use/ongoing use; cut-off $cocaine_{total}$ ceased use at follow-up <0.5 ng/mg)(for a detailed subgroup description, see **Table S6**). Given the lack of power in such a four-group comparison, the mixed ANCOVA (corrected for ADHD) displayed only non-significant group*time interactions regarding all domains, but with some interesting effect sizes: GCI ($F_{3,33}$=1.70, p=.19, $_p\eta^2$=.13), attention ($F_{3,33}$=2.09, p=.12, $_p\eta^2$=.16), working memory ($F_{3,33}$=1.89, p=.15, $_p\eta^2$=.15), declarative memory ($F_{3,33}$=1.69, p=.19, $_p\eta^2$=.13), and executive functions ($F_{3,33}$=0.22, p=.88, $_p\eta^2$=.02). As we were specifically interested in whether long-term cocaine abstinence has an effect on cognition, we interpreted Sidak pre-post comparisons in the group of ceasing cocaine users. Notably, users who completely stopped cocaine use for at least six months (negative hair toxicology) displayed a significantly improved GCI (p<.05, d=0.93), attention (p<.05, d=1.10), and declarative memory (p<.05, d=.65), resulting in follow-up test scores in the range of the control group (**Figure 3**).

An ADHD-corrected mixed ANCOVA of the GCI including only cocaine *increasers* stratified according to positive (n=12) and negative cocaine urine toxicologies (n=7) at baseline and follow-up did not reveal a significant group*time interaction ($F_{1,16}$=0.00, p=.99, $_p\eta^2$=.00), indicating that recent cocaine use likely did not explain the decline in test performance in *increasers* (**Figure S3**). Because only one cocaine *decreaser* featured a positive urine toxicology analysis at the follow-up, we did not analyze the group of *decreasers* further.

Discussion

This longitudinal study is the first linking objectively quantified changes in cocaine use patterns during one year with the development of cognitive performance. Hair toxicology analyses allowed a precise drug use quantification to detect changes across the test interval and ensured the inclusion of participants with relatively little polytoxic drug use.

This study yielded several major findings: First, *increased* cocaine use was associated with additional cognitive decline within one year, particularly in working memory, supporting the hypothesis that these cognitive impairments were partially cocaine-induced, as recent animal studies have implied (Gould *et al*, 2012; Liu *et al*, 2008; Olausson *et al*, 2007; Porter *et al*, 2011). This finding is also in line with previous cross-sectional studies showing that the extent, duration, and amount of cocaine use are related to the severity of cognitive dysfunction (Bolla *et al*, 1999; Colzato *et al*, 2007; Vonmoos *et al*, 2013). Second, *decreased* cocaine use within one year was linked to small but consistent cognitive improvements in all four domains confirming the assumption from previous cross-sectional and longitudinal studies that cognitive consequences from crack cocaine use might be partially reversible (De Oliveira *et al*, 2009; Di Sclafani *et al*, 2002). Users with moderate lifetime exposure who completely ceased their cocaine consumption seemed to recover entirely and attained a similar attention, memory, and global cognitive performance as controls in the follow-up. Because chronic cocaine administration to rhesus monkey produced neuroadaptations in dopamine systems (Letchworth *et al*, 2001; Nader *et al*, 2002), the reversibility of cognitive deficits after sustained abstinence suggests that neuroplastic adaptations might be restored if the repeated pharmacological stimulus is discontinued. Third, correlations between the cumulative cocaine dose used during the test interval and cognitive change scores, further support the hypothesis that cognitive decline might be drug-induced. Moreover, a substantial correlation between the age of cocaine use onset and change in working memory performance in *decreasers* indicates that early onset might be a risk factor for sustained cognitive impairment after chronic cocaine use.

Users with escalating cocaine use displayed the largest cognitive decrements in working memory, confirming findings from our larger cross-sectional sample (Vonmoos *et al*, 2013) and from a meta-

analysis (Jovanovski *et al*, 2005) that this domain is strongly affected in dependent cocaine users. The working memory domain was also improved if cocaine consumption was considerably decreased. These data suggest that either working memory is most susceptible to cocaine effects, as it has previously been associated with monoamine functioning (Robbins and Arnsten, 2009), or working memory tasks are the most reliable and sensitive test parameters. In fact, among controls, the test-retest reliability of the declarative memory (r=.80), GCI (r=.78), and working memory (r=.77) was superior compared with executive function (r=.59) and attention (r=.55).

Overall, the cognitive changes in our longitudinal study appear to be relatively small. However, at baseline, the *increaser* group already had a cumulative lifetime cocaine dose of 1.2kg – a level at which most cocaine users already display substantial cognitive impairments (Vonmoos *et al*, 2013). Given that the *increasers* reported an additional cumulative cocaine dose of 90g, used between baseline and follow-up, this amount might have been too small to exert additional and measurable cognitive decrements (in conjunction with possible ceiling effects).

The putative reversibility of cognitive impairments in *decreasers*, particularly in working memory and declarative memory, confirms the results of two previous studies indicating memory improvements in cocaine users at six-months abstinence (De Oliveira *et al*, 2009; Di Sclafani *et al*, 2002). However, one study (De Oliveira *et al*, 2009) had a cross-sectional design, whereas the other (Di Sclafani *et al*, 2002) postulated improvements but did not correct for test-retest effects. Another study (van Gorp *et al*, 1999) with cocaine users (n=37) found lasting detrimental effects in nonverbal declarative memory but small improvements in a verbal declarative memory test after 45 days of drug abstinence – a finding similar to the RAVLT results in our study. Moreover, a study with cocaine users (n=30) at one month of drug abstinence found no significant differences in learning and delayed recall compared with controls (Bolla *et al*, 1999). Because dependent cocaine users exhibited reduced activity in frontal regions (Volkow *et al*, 2009) crucial for cognitive functioning (Cabeza and Nyberg, 2000) and given that these reductions persisted at least three to four months after detoxification (Volkow *et al*, 1992), the abstinence duration in the last two studies mentioned here was supposedly too brief to reveal cognitive recovery effects.

The cognitive recovery process seemed to be particularly pronounced in users who ceased taking cocaine; at follow-up, all off these users had a GCI score within one SD of the control group. However, cocaine users who had been abstinent for at least six months also reported a relatively low cumulative lifetime dose of cocaine (0.7kg) compared with users with decreased but ongoing cocaine use (5.9kg). Because the abstinent user group did not significantly differ from the other cocaine use subgroups in terms of age, sex, verbal IQ, education, and ADHD, their putatively higher cognitive performance might be probably explained by this lower baseline use of cocaine. Nonetheless, it remains unclear if the subjects in this group became abstinent because of their higher overall functioning, or whether there is a "point of no return" none of these subjects attained (i.e., a cumulative cocaine dose beyond which no full recovery can be expected). Nevertheless, we propose that the reversibility of cognitive functions in cocaine users (1) takes some time (at least several months), (2) differs among cognitive domains, (3) depends on the residual level of cocaine use, and (4) is probably related to the amount of lifetime cumulative cocaine dose and age of onset.

This study has some limitations. First, although the group assignment was based on objective hair toxicology covering the last six months, for the first six months of the time interval we could rely only on self-reports. Second, the importance of hair melanin pigment for the incorporation of cocaine into the hair structure has not been conclusively clarified (Mieczkowski and Newel, 2000). However, because there is no apparent melanin effect regarding cocaine (Mieczkowski and Kruger, 2007), and 30 of 38 cocaine users in the present study had brownish hair, it is unlikely that the group assignment was affected by this potential constraint. We also used a within-subject design, and, thus, inter-individual differences in hair color should play a minor role. Third, our executive function domain comprised only two parameters because we excluded the CANTAB IED from follow-up testing. Future longitudinal studies might therefore employ a more comprehensive neuropsychological test battery focusing on executive functioning. Fourth, although our sample consists of cocaine users with relatively little polytoxic drug use, it should be mentioned that at baseline, cocaine *increasers* displayed a small but significantly higher use of MDMA (0.04 vs. 0.01 tablets per week) and longer use of amphetamine (3.3 vs. 1.3 years) than *decreasers*. Furthermore, at follow-up cocaine *increasers* revealed a slightly higher use of MDMA and methylphenidate compared to baseline and featured an

additional rise in weekly alcohol use. Whereas the change in MDMA use was less than half a tablet per week, the difference in methylphenidate consumption was explained by a single individual. The rise in weekly alcohol use was based on an increased intake in three of 19 cocaine *increasers*. However, exclusion of the single methylphenidate user and the alcohol increasing subjects did not change the main results in separate analyses. Thus, although changes in other drugs should be considered as a contributing factor to our results, it seems reasonable that compared to the strong increase in cocaine use, the effect of changed use of other drugs is likely rather small.

In conclusion, our findings suggest that cognitive performance co-varies with changing cocaine use within a one-year period. Whereas increased cocaine use was associated with further decrements of cognitive functioning (most pronounced in working memory), decreased cocaine use was linked to improved cognition, particularly in attention and the memory domains. Remarkably, cocaine users who completely ceased their consumption attained the same cognitive performance level as the controls. However, early age of cocaine use onset seem to hamper these recovery processes, at least in the working memory, which is a highly relevant finding for prevention and harm reduction interventions. While previous research has discussed the possibility of neuroenhancement in stimulant users by drugs (Sofuoglu *et al*, 2013), our findings suggest that drug abstinence might be the best way to recover cognitive performance in stimulant users as abstinence has obviously a more beneficial side-effect profile than any psychopharmacological intervention. Although it has been shown that stimulant treatment can improve cognitive performance in cocaine users at least acutely (Sofuoglu *et al*, 2013), the use of prescription stimulants to treat cognitive deficits in stimulant users might be questioned given that methylphenidate and amphetamines likely produce or even prolong neuroplasticity induced by cocaine or other illegal stimulants as they have similar mechanisms of action (Svetlov *et al*, 2007). However, the chronic effect or the discontinuation of pro-cognitive stimulant treatment on cognition of cocaine users has not been investigated so far. Finally, the general reversibility of cognitive deficits also indicates that drug-induced neuroadaptations can probably be remodulated by psychotherapeutical or pharmacological interventions, which might help to achieve and maintain abstinence.

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Table 1. Demographic data and pattern of cocaine use.

	Baseline (t1)							1-year follow-up (t2)[m]						
	Controls (n=48)	Cocaine Increaser (n=19)	Cocaine Decreaser (n=19)	F/χ^2/T	df, df_{err}	p	Effect size	Controls (n=48)	Cocaine Increaser (n=19)	Cocaine Decreaser (n=19)	F/χ^2/T	df, df_{err}	p	Effect size
Age, y	30.3 (8.9)	31.5 (9.4)	31.4 (8.3)	.20[a]	2,83	.82	$_p\eta^2$=.00							
Sex (f/m)	16/32	3/16	5/14	2.11[b]	2	.35	V=.16							
Verbal IQ (MWT-B)[d]	107.6 (10.0)	102.9 (9.7)	103.8 (7.1)	2.20[a]	2,83	.12	$_p\eta^2$=.05							
Education, y	10.8 (1.8)	10.4 (1.8)	10.0 (1.5)	1.30[a]	2,83	.28	$_p\eta^2$=.03							
ADHD-SR score (0-22)	7.7 (5.2)	13.5 (9.4)**	14.1 (6.8)**	8.83[a]	2,83	**<.001**	$_p\eta^2$=.18							
ADHD DSM IV (y/n)[e]	0/48	4/15	3/16	7.02[b]	2	**.03**	V=.28							
Weeks between t1 and t2	58.2 (10.1)	59.3 (12.1)	61.9 (14.5)	.69[a]	2,83	.50	$_p\eta^2$=.02							
BDI score (0-63)	3.5 (3.3)	7.3 (8.0)*	8.7 (6.5)**	7.53[a]	2,83	**<.001**	$_p\eta^2$=.15							
BDI depression (y/n)[g]	0/48	1/18	1/18	2.59[b]	2	.27	V=.17							
Cocaine														
Times per week[h]	-	1.6 (1.8)	1.0 (1.3)	1.17[c]	36	.25	d=.38	-	1.1 (0.8)	0.3 (0.3)	3.85[c]	36	**<.001**	d=1.32
Grams per week[h]	-	2.0 (2.5)	1.7 (2.3)	.41[c]	36	.68	d=.12	-	1.6 (2.5)	0.4 (0.4)	2.18[c]	36	**.04**	d=.67
Years of use	-	7.0 (5.5)	8.2 (5.4)	.68[c]	36	.50	d=.22	-	8.9 (5.4)	9.7 (5.2)	.45[c]	36	.65	d=.15
Max. dose (grams/day)[k]	-	4.7 (4.4)	5.9 (6.4)	.71[c]	36	.48	d=.22	-	3.7 (2.5)	3.1 (2.8)	.63[c]	36	.53	d=.23
Cumulative dose (grams)[k]	-	1182 (1635)	3698 (8585)	1.25[c]	36	.22	d=.41	-	91 (119)	49 (89)	1.25[c]	36	.22	d=.40
Last consumption (days)	-	18.5 (25.1)	16.8 (14.6)	.29[c]	36	.77	d=.08	-	7.0 (6.3)	81.4 (145.1)	2.23[c]	36	**.03**	d=.72
Cocaine craving (0-70)[i]	-	19.8 (9.5)	17.7 (7.2)	.79[c]	36	.44	d=.25	-	20.5 (10.8)	15.8 (6.2)	1.66[c]	36	.11	d=.53
Hair analysis (ng/mg)[l]														
$Cocaine_{total}$	-	10.3 (29.2)	14.9 (32.2)	.46[c]	36	.65	d=.15	-	40.7 (76.1)	4.2 (8.2)	2.08[c]	36	**.05**	d=.67
Cocaine	-	8.2 (23.3)	11.4 (23.9)	.42[c]	36	.68	d=.14	-	31.7 (56.5)	3.1 (5.9)	2.19[c]	36	**.03**	d=.71
Benzoylecgonine	-	1.9 (5.5)	3.1 (7.6)	.58[c]	36	.56	d=.18	-	8.3 (19.6)	1.0 (2.2)	1.62[c]	36	.11	d=.52
Cocaethylene	-	1.0 (2.8)	0.9 (2.8)	.11[c]	36	.91	d=.04	-	1.2 (2.1)	0.3 (1.0)	1.56[c]	36	.13	d=.55
$Norcocaine_t$	-	0.2 (0.5)	0.4 (0.8)	.83[c]	36	.41	d=.30	-	0.6 (1.4)	0.1 (0.1)	1.71[c]	36	.10	d=.50
Urine toxicology (n/p)[k]	48/0	14/5	16/3	.63[b]	1	.43	V=.13	48/0	7/12	18/1	14.15[b]	1	**<.001**	V=.61
Alcohol[n]														
Grams per week[h]	119.9 (136.8)	169.4 (129.2)	155.3 (146.4)	1.07[a]	2,83	.35	$_p\eta^2$=.03	104.3 (88.6)	259.7 (244.5)***	127.4 (141.4)°	7.71 [a]	2,83	**<.001**	$_p\eta^2$=.16
Years of use	13.3 (8.8)	13.7 (7.6)	12.0 (7.3)	.23[a]	2,83	.79	$_p\eta^2$=.01	14.0 (8.7)	14.8 (7.5)	12.6 (7.9)	.34[a]	2,83	.71	$_p\eta^2$=.01
Nicotine[n]														
Smoking (y/n)[f]	37/11	14/5	14/5	.13[b]	2	.94	V=.04	40/8	15/4	13/6	1.83[b]	2	.40	V=.15
Cigarettes per day[h]	8.7 (8.7)	12.8 (11.2)	9.5 (8.2)	1.38[a]	2,83	.26	$_p\eta^2$=.03	8.2 (8.7)	13.4 (12.0)	8.2 (7.8)	2.31[a]	2,83	.11	$_p\eta^2$=.05
Years of use	9.3 (8.3)	10.4 (8.9)	12.7 (10.3)	.95[a]	2,83	.39	$_p\eta^2$=.02	10.5 (8.8)	12.5 (8.6)	12.6 (9.9)	.56[a]	2,83	.57	$_p\eta^2$=.01

Cannabis[n]														
Grams per week[h]	0.6 (1.6)	3.3 (8.9)	1.2 (2.3)	2.38[a]	2,83	.10	$_p\eta^2$=.05	0.5 (1.6)	2.1 (4.6)	1.1 (2.7)	2.28[a]	2,83	.11	$_p\eta^2$=.05
Years of use	4.5 (4.9)	9.5 (8.5)*	10.1 (9.7)*	5.92[a]	2,83	**.004**	$_p\eta^2$=.12	4.6 (5.9)	10.5 (9.8)*	8.6 (9.7)	4.64[a]	2,83	**.01**	$_p\eta^2$=.10
Cumulative dose (grams)	980 (3985)	3199 (5899)	2606 (6359)	1.61[a]	2,83	.21	$_p\eta^2$=.04	53.4 (180)	217.8 (526.5)	84.7 (189.6)	2.15[a]	2,83	.12	$_p\eta^2$=.05
Last consumption (days)[j]	39.3 (1.6);n=22	10.0 (0.4);n=14	25.4 (1.1);n=12	2.19[a]	2,45	.12	$_p\eta^2$=.09	36.5 (1.5);n=22	9.7 (0.4);n=13	50.8 (2.1);n=10	1.20[a]	2,42	.31	$_p\eta^2$=.05
Urine toxicology (n/p)[k]	42/6	15/4	14/5	2.03[b]	2	.36	V=.15	42/6	7/12	15/4	18.61[b]	2	**<.001**	V=.47
Amphetamine[n]														
Grams per week[h]	0.0 (0.1)	0.1 (0.1)**	0.0 (0.1)	5.18[a]	2,83	**.008**	$_p\eta^2$=.11	0.0 (0.0)	0.1 (0.2)**	0.0 (0.1)	5.89[a]	2,83	**.004**	$_p\eta^2$=.12
Years of use	0.0 (0.0)	3.3 (4.0)***	1.3 (3.1)°	13 .73[a]	2,83	**<.001**	$_p\eta^2$=.25	0.1 (0.5)	3.2 (4.9)**	2.7 (5.5)*	7.46[a]	2,83	**.001**	$_p\eta^2$=.15
Cumulative dose (grams)	0.0 (0.1)	56.0 (177.6)*	16.2 (35.9)	2.99[a]	2,83	.06	$_p\eta^2$=.07	0.0 (0.1)	4.4 (8.9)**	1.4 (3.5)	6.47[a]	2,83	**.002**	$_p\eta^2$=.13
Last consumption (days)[j]	121.6 (5.1);n=1	73.6 (3.1);n=10	90.9 (3.8);n=3	.29[a]	2,11	.75	$_p\eta^2$=.05	17.5 (0.7);n=1	35.7 (1.5);n=8	99.8 (4.2) ;n=4	1.48[a]	2,10	.27	$_p\eta^2$=.23
Hair analysis (ng/mg)	0.0 (0.0)	0.1 (0.2)*	0.0 (0.0)	4.35[a]	2,83	**.02**	$_p\eta^2$=.09	0.0 (0.0)	0.1 (0.2)	0.1 (0.2)	2.89[a]	2,83	.06	$_p\eta^2$=.07
MDMA[n]														
Tablets per week[h]	0.0 (0.0)	0.0 (0.1)***	0.0 (0.0)°	7.42 [a]	2,83	**.001**	$_p\eta^2$=.15	0.0 (0.0)	0.4 (0.9)**	0.0 (0.0)°	5.54 [a]	2,83	**.006**	$_p\eta^2$=.12
Years of use	0.3 (1.0)	3.5 (4.5)***	2.4 (4.6)*	8.42[a]	2,83	**<.001**	$_p\eta^2$=.17	0.2 (1.4)	3.8 (5.5)**	3.2 (5.6)*	7.78[a]	2,83	**<.001**	$_p\eta^2$=.16
Cumulative dose (tablets)	1.3 (4.0)	108.8 (249.7)**	18.7 (46.2)	5.71[a]	2,83	**.005**	$_p\eta^2$=.12	0.2 (0.8)	17.0 (49.3)*	2.8 (5.2)	3.67[a]	2,83	**.03**	$_p\eta^2$=.08
Last consumption (days)[j]	5.0 (0.2);n=1	89.9 (3.7);n=7	40.2 (1.7);n=4	1.63[a]	2,9	.25	$_p\eta^2$=.27	91.2 (3.8);n=3	41.6 (1.7);n=6	47.8 (2.0);n=5	1.11[a]	2,11	.36	$_p\eta^2$=.17
Hair analysis (ng/mg)	0.0 (0.0)	0.3 (0.7)	0.4 (1.5)	2.23[a]	2,83	.11	$_p\eta^2$=.05	0.0 (0.0)	0.5 (0.8)***	0.1 (0.3)	7.87[a]	2,83	**<.001**	$_p\eta^2$=.16
GHB[n]														
Cumulative dose (pipettes)	0.0 (0.0)	0.5 (0.7)	0.5 (1.7)	3.36[a]	2,83	**.04**	$_p\eta^2$=.07	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	-	-	-	-
Hallucinogens[n]														
Cumulative dose (times)	0.9 (2.2)	27.9 (72.8)*	9.9 (22.9)	3.92[a]	2,83	**.02**	$_p\eta^2$=.09	0.0 (0.0)	1.1 (1.6)***	0.6 (1.5)	8.57[a]	2,83	**<.001**	$_p\eta^2$=.17
Methlyphenidate[n]														
Cumulative dose (tablets)	0.0 (0.0)	20.2 (60.4)*	0.5 (2.3)	3.76[a]	2,83	**.03**	$_p\eta^2$=.08	0.0 (0.1)	67.7 (239.5)	0.3 (0.6)	2.72[a]	2,83	.07	$_p\eta^2$=.06
Hair analysis (ng/mg)	0.0 (0.0)	0.0 (0.1)	0.0 (0.0)	1.80[a]	2,83	.17	$_p\eta^2$=.04	0.0 (0.0)	0.1 (0.2)*	0.0 (0.0)	3.62[a]	2,83	**.03**	$_p\eta^2$=.08

Means and standard deviations. Significant p values are shown in bold.
[a] ANOVA (all groups, with significant Sidak post-hoc test vs. control group: *p<.05; **p<.01; ***p<.001; vs. cocaine increaser: °*p*<.05). [b] χ^2-test (all groups/cocaine users only) for frequency data. [c] Independent *t*-test (cocaine users only). [d] Verbal IQ was assessed by the Mehrfachwahl Wortschatz Intelligenztest (Lehrl, 1999). [e] ADHD-SR, ADHD self rating scale (cut-off DSM-IV criteria)(Roesler *et al*, 2004). [f] Smoking habits were assessed by the Fagerstroem Test of Nicotine Dependence (Heatherton *et al*, 1991). [g] BDI, Beck Depression Inventory (cut-off ≥18)(Hautzinger *et al*, 1994). [h] Average use during the last 6 months. [i] Craving for cocaine was assessed by the Brief-CCQ (Sussner *et al*, 2006). [j] Last consumption is averaged only for persons who used the drug in the last 6 months. [k] Urine toxicology (neg/pos) are based on cut-off value for Cocaine = 150 ng/ml and for Tetrahydrocannabinol 50 ng/ml (Substance Abuse and Mental Health Services Administration, 2008). The χ^2-test for cocaine includes only cocaine users, the χ^2-test for cannabis includes controls and cocaine users. [l] Hair samples were voluntary and data are missing for three controls. [m] Parameters at follow-up refer to the 1-year period between t1 and t2. [n] At baseline, average use during the last 6 months. Use frequency, duration of use, and cumulative doses are averaged within the total group.

Table 2. Domain scores at the baseline (t1) and the 1-year follow-up (t2).

	Baseline (t1)							1-year follow-up (t2)						
	Controls (n=48)	Cocaine Increaser (n=19)	Cocaine Decreaser (n=19)	F[a]	df, df_{err}	p	Part. Eta^2	Controls (n=48)	Cocaine Increaser (n=19)	Cocaine Decreaser (n=19)	F[a]	df, df_{err}	p	Part. Eta^2
Global Cognitive Index	0.00 (0.54)	-0.52 (0.77)*	-0.46 (0.73)*	6.26	2,83	**.003**	.13	0.24 (0.58)	-0.36 (0.84)**	-0.07 (0.72)	5.85	2,83	**.004**	.12
Neurocognitive domains														
Attention	0.00 (0.78)	-0.45 (0.85)	-0.41 (0.87)	2.94	2,83	.06	.07	0.29 (0.84)	-0.18 (0.91)	0.04 (0.83)	2.19	2,83	.12	.05
Working memory	0.00 (0.70)	-0.46 (0.91)	-0.47 (0.69)	4.09	2,83	**.02**	.09	0.24 (0.64)	-0.44 (0.80)**	-0.14 (0.69)	7.17	2,83	**.001**	.15
Declarative memory	0.00 (0.76)	-0.60 (1.12)	-0.44 (1.11)	3.42	2,83	**.04**	.08	0.20 (0.66)	-0.53 (1.19)*	-0.02 (1.21)	4.10	2,83	**.02**	.09
Executive functions	0.00 (0.70)	-0.58 (1.11)*	-0.52 (0.96)	4.36	2,83	**.02**	.10	0.25 (0.79)	-0.31 (1.19)	-0.18 (0.65)	3.46	2,83	**.04**	.08

Means and standard deviations. Significant p values are shown in bold.
[a] ANOVA (all groups, with significant Sidak post-hoc test vs. control group: *p<.05; **p<.01; ***p<.001).
Global cognitive index and cognitive domain scores are z-transformed values. Z-score transformation is based on control group mean and variance at baseline.

Figure legends

Figure 1: Development of cognitive functioning in cocaine *increasers* and *decreasers* within one year. *Z*-scores and SE for the cognitive domains (corrected for ADHD). Z-score transformation was based on control group mean and standard deviation at baseline. Follow-up values were adjusted for the test-retest effect. Change in cognitive test performance from the baseline (t1) to the one-year follow-up (t2): Sidak post-hoc tests (*p<.05). GCI: increaser p=.36, d=-0.21, decreaser p=.14, d=0.33. Attention: increaser p=.87, d=-0.04, decreaser p=.30, d=0.22. Working memory: increaser p<.05, d=-0.52, decreaser p=.34, d=0.21. Declarative memory: increaser p=.44, d=-0.16, decreaser p=.21, d=0.30. Executive functions: increaser p=.92, d=0.02, decreaser p=.52, d=0.14.

Figure 2: Correlation of age of cocaine use onset and working memory change scores ($\Delta_{t2\text{-}t1}$) in decreasing cocaine users (n=19). Pearson product-moment correlation (two-tailed): r=.54, p<.05. Working memory change scores were adjusted for the test-retest effect.

Figure 3: Cognitive functions in low/high cocaine *increasers* and *decreasers* with ongoing/ceased cocaine use within one year. *Z*-scores and SE for the cognitive domains (corrected for ADHD). Z-score transformation was based on control group mean and standard deviation at baseline. Follow-up values were adjusted for the test-retest effect. Change in cognitive test performance from the baseline (t1) to the one-year follow-up (t2): Sidak post-hoc tests (*p<.05). GCI: $\text{increaser}_{\text{low}}$ p=.61, d=-0.14, $\text{increaser}_{\text{high}}$ p=.41, d=-0.30, $\text{decreaser}_{\text{ongoing}}$ p=.82, d=0.06, $\text{decreaser}_{\text{ceasing}}$ p<.05, d=0.93. Attention: $\text{increaser}_{\text{low}}$ p=.41, d=0.29, $\text{increaser}_{\text{high}}$ p=.23, d=-0.46, $\text{decreaser}_{\text{ongoing}}$ p=.74, d=-0.08, $\text{decreaser}_{\text{ceasing}}$ p<.05, d=1.10. Working memory: $\text{increaser}_{\text{low}}$ p<.05, d=-0.60, $\text{increaser}_{\text{high}}$ p=.52, d=-0.42, $\text{decreaser}_{\text{ongoing}}$ p=.58, d=0.20, $\text{decreaser}_{\text{ceasing}}$ p=.42, d=0.22. Declarative memory: $\text{increaser}_{\text{low}}$ p=.90, d=-0.04, $\text{increaser}_{\text{high}}$ p=.30, d=-0.29, $\text{decreaser}_{\text{ongoing}}$ p=.99, d=-0.01, $\text{decreaser}_{\text{ceasing}}$ p<.50, d=0.65. Executive functions: $\text{increaser}_{\text{low}}$ p=.70, d=-0.09, $\text{increaser}_{\text{high}}$ p=.54, d=0.46, $\text{decreaser}_{\text{ongoing}}$ p=.63, d=0.12, $\text{decreaser}_{\text{ceasing}}$ p=.68, d=0.17.

Figure 1

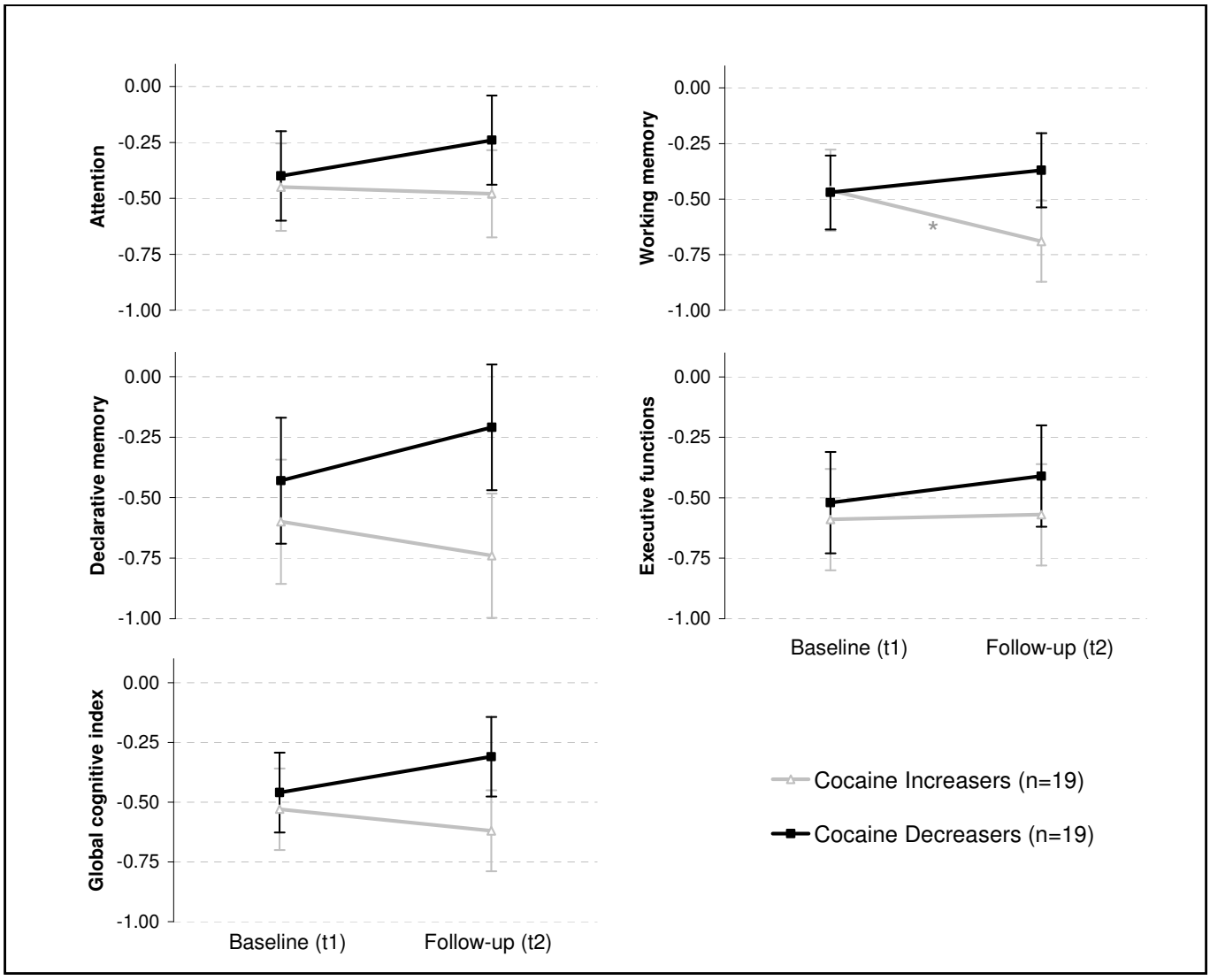

Attention
Working memory
Declarative memory
Executive functions
Global cognitive index
0.00
-0.25
-0.50
-0.75
-1.00
*
Baseline (t1)
Follow-up (t2)
Cocaine Increasers (n=19)
Cocaine Decreasers (n=19)

Figure 2

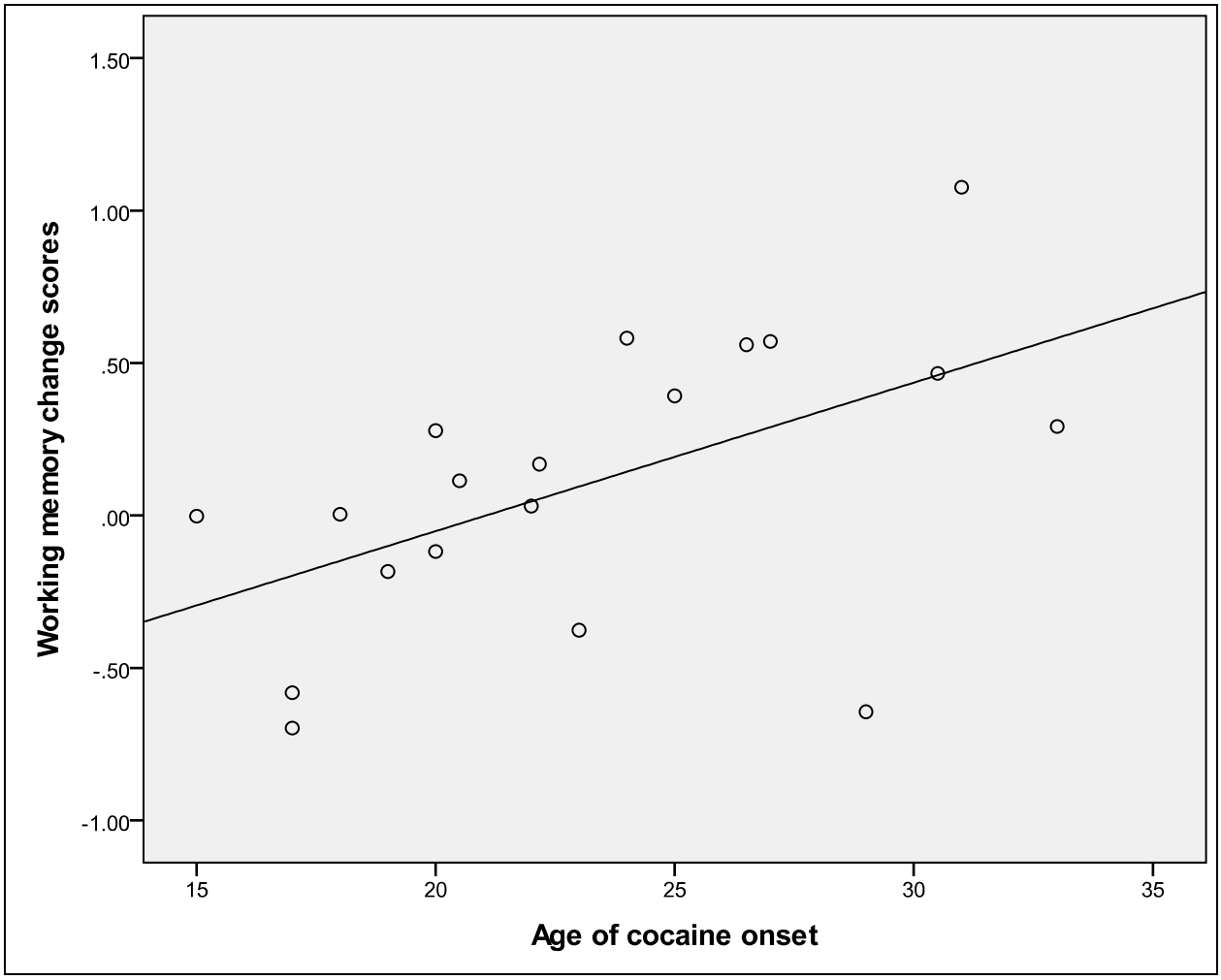
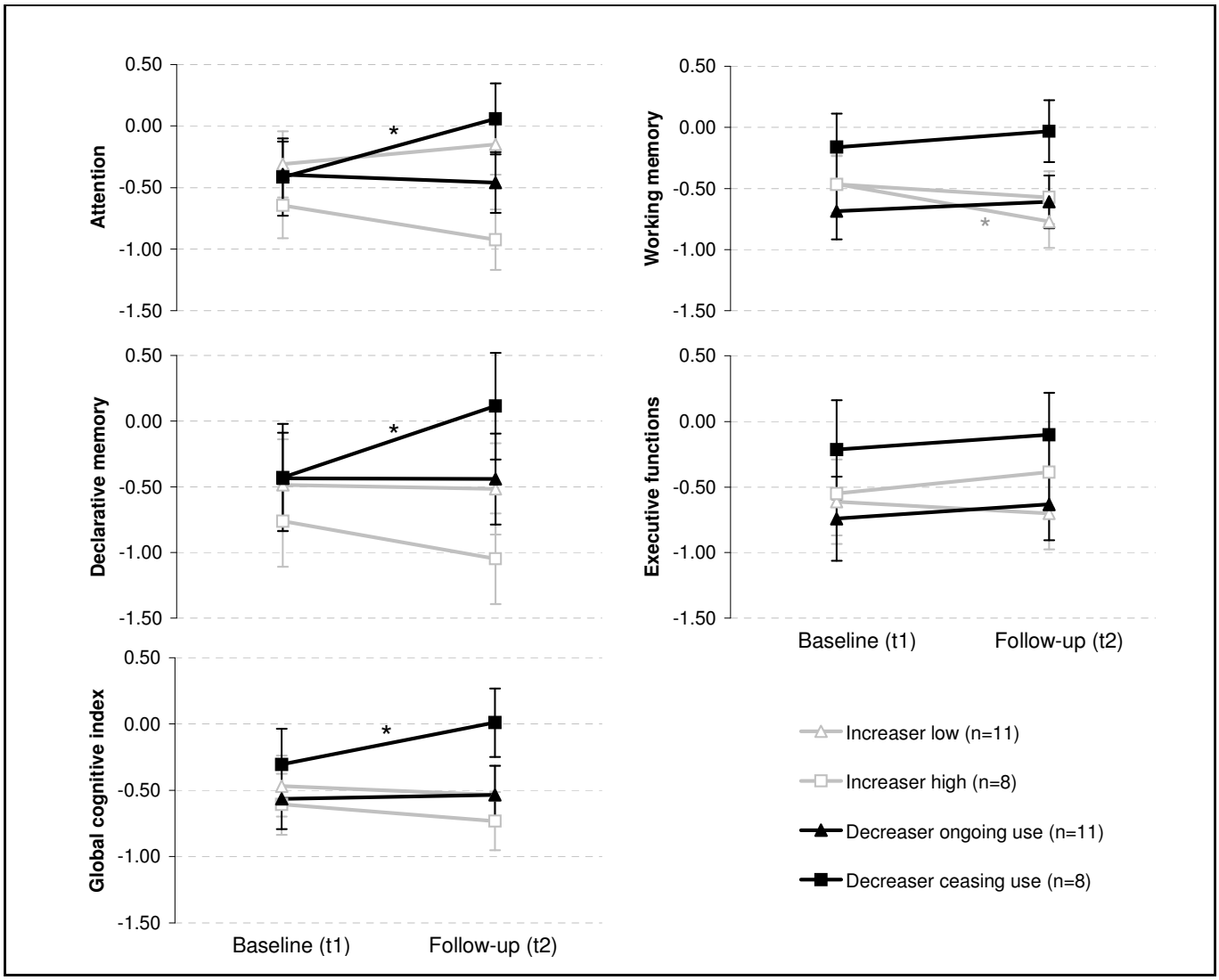

Working memory change scores
1.50
1.00
.50
.00
-.50
-1.00
15
20
25
30
35
Age of cocaine onset

Figure 3


Attention
Working memory
Declarative memory
Executive functions
Global cognitive index
0.50
0.00
-0.50
-1.00
-1.50
*
Baseline (t1)
Follow-up (t2)
Increaser low (n=11)
Increaser high (n=8)
Decreaser ongoing use (n=11)
Decreaser ceasing use (n=8)

Supplementary Material

Vonmoos M, Hulka LM, Preller KH, Minder F, Baumgartner MR, Quednow BB.
Cognitive impairment in cocaine users is drug-induced but partially reversible:
evidence from a longitudinal study

Methods S1. Recruitment and selection.

The recruitment focused on the greater area of Zurich and lasted from January 2010 (start recruitment) until March 2013 (finish of the follow-up). Participants were recruited via advertisements in local newspapers, online media, drug prevention and treatment centers, psychiatric hospitals, and by word of mouth. Eight-hundred-and-four prospective participants underwent a standardized telephone interview, whereof 240 subjects were tested in the cross-sectional study. Six participants were not re-invited to participate in the follow-up study (refusal study participation, psychiatric disorders or first-grade family member with schizophrenia). The remaining 234 participants (138 cocaine users, 96 controls) were contacted and invited for a follow-up test session twelve months after baseline testing. One-hundred-and-two participants (59 cocaine users, 43 controls) were not available for the follow-up study due to different reasons (not answering, losing interest, time reasons, death). One-hundred-and-thirty-two participants (56%; 79 cocaine users, 53 controls) agreed to be re-tested and participated in the follow-up. Twenty-seven of these subjects (22 cocaine users, 5 controls) had to be excluded from the final analyses due to hair analyses revealing illegal drug use not allowed by our exclusion criteria (e.g., opioids or excessive MDMA intake) or due to starting use of psychotropic medication (e.g., antipsychotics or antidepressants).

Methods S2. Construction of cognitive domain scores.

Thirteen predefined main cognitive test parameters were z-transformed on the basis of means and standard deviations of the control group (n=48) at t1. If necessary, test scores were reversed so that high scores always indicated a better cognitive performance. These parameters were reduced to the four cognitive domains attention, working memory, declarative memory, and executive functions according to theoretical a priori considerations and in accordance with previous literature findings as cited below. Furthermore, the four z-scored domains were equally integrated into a broad global cognitive index (GCI). Apart from the non-consideration of two CANTAB Intra/Extradimensional Set Shifting Task (IED) parameters, we used exactly the same approach as in the previously published cross-sectional study (Vonmoos *et al*, 2013).

Attention
To assess attention, we primarily focused on sustained attention by including the two RVP parameters discrimination performance A' and total of hits (Jones *et al*, 1992). In order to diversify this domain, we further added the RAVLT parameter trial 1, a supraspan measure with a strong attentional component (Lezak *et al*, 2004).

Working memory
The SWM parameter total errors tested the capability to retain spatial information and to manipulate remembered items in the working memory (Morris *et al*, 1988). The LNST score measured verbal working memory by summing up the number of correct responses (Wechsler, 1997). The PAL first trial memory score measured visual working memory by counting the number of correctly located patterns after the first presentation (Sahakian *et al*, 1988).

Declarative memory
Three RAVLT parameters were included to assess the verbal declarative memory performance: ∑trials 1-5, delayed recall trial 7, and adjusted recognition performance p(A). Furthermore, the two PAL parameters (adjusted total of errors and adjusted total of trials) were used to capture visual declarative memory (Sahakian *et al*, 1988).

Executive functions
Because we excluded the CANTAB IED from the longitudinal analysis due to an evident ceiling effect at baseline (Vonmoos *et al*, 2013), the executive functions were measured by only two parameters. First, the SWM strategy score assessed the applied heuristic strategies (Morris *et al*, 1988), a typical feature of the executive functions. Second, the RAVLT recall consistency score is a parameter typically impaired in patients with prefrontal lesions (Benedict *et al*, 2005; Jokeit *et al*, 1997) and related with measures of executive functions (Beebe *et al*, 2000).

Table S1. Demographic data and pattern of drug use for the cocaine user group with a *stable* use pattern.

	Baseline (t1)	1-year follow-up (t2)[h]
Age, y	27.0 (5.6)	
Sex (f/m)	8/11	
Verbal IQ (MWT-B)[a]	104.5 (9.1)	
Education, y	10.3 (1.6)	
ADHD-SR score (0-22)	14.4 (10.2)	
ADHD DSM IV (y/n)[b]	4/15	
Weeks between t1 and t2	64.8 (16.3)	
BDI score (0-63)	8.1 (6.2)	
BDI depression (y/n)[d]	2/17	
Cocaine		
Times per week[e]	0.6 (0.6)	0.3 (0.2)
Grams per week[e]	0.7 (0.6)	0.2 (0.3)
Years of use	5.4 (5)	6.3 (5.6)
Max. dose (grams/day)[k]	3 (3.1)	1.7 (1.5)
Cumulative dose (grams)[k]	394.4 (563)	18.3 (25.4)
Last consumption (days)	42.2 (49.7)	58.2 (116.6)
Cocaine craving (0-70)[f]	18.4 (7.7)	15.1 (7.7)
Hair analysis, ng/mg		
$Cocaine_{total}$	3.2 (9.9)	3.2 (9.4)
Cocaine	2.5 (7.6)	2.6 (7.9)
Benzoylecgonine	0.6 (1.9)	0.4 (1.2)
Cocaethylene	0.3 (0.8)	0.7 (2.1)
Benzoylecgonine	0.1 (0.3)	0.1 (0.3)
Urine toxicology (n/p)[g]	18/1	16/3
Alcohol[k]		
Grams per week[e]	132.3 (86.4)	146.7 (95.1)
Years of use	9.9 (5.0)	11.1 (5.5)
Nicotine[k]		
Smoking (y/n)[c]	14/5	15/4
Cigarettes per day[e]	12.2 (8.3)	12.7 (8.9)
Years of use	9.2 (6.3)	9.5 (6.7)
Cannabis[k]		
Grams per week[e]	1.2 (2.6)	0.9 (1.6)
Years of use	7.8 (5.9)	8.4 (6.2)
Cumulative dose (grams)	1932.7 (4309.1)	55.0 (94.7)
Last consumption (days)[i]	28.7 (41.1);n=15	18.7 (33.1);n=13
Urine toxicology (n/p)[g]	16/3	15/4
Amphetamine[k]		
Grams per week[e]	0.0 (0.1)	0.0 (0.1)
Years of use	1.4 (3.0)	1.9 (3.5)
Cumulative dose (grams)	2.8 (5.8)	1.9 (6)
Last consumption (days)[i]	61.8 (59.6);n=7	65.9 (23.2);n=3
Hair analysis ng/mg	0.0 (0.0)	0.0 (0.0)
MDMA[k]		
Tablets per week[e]	0.0 (0.0)	0.1 (0.1)
Years of use	2.1 (3.8)	2.6 (4.3)
Cumulative dose (tablets)	14.6 (39.9)	4.3 (7.1)
Last consumption (days)[i]	56.4 (43.4);n=6	69.7 (36.4);n=8
Hair analysis ng/mg	0.2 (0.5)	0.2 (0.4)
GHB[k]		
Cumulative dose (pipettes)	4.5 (17.8)	1.2 (5.2)
Hallucinogens[k]		
Cumulative dose (times)	6.3 (14.3)	0.4 (0.8)
Methlyphenidate[k]		
Cumulative dose (tablets)	41.3 (144.6)	1.5 (4.6)
Hair analysis ng/mg	0.0 (0.0)	0.0 (0.0)

Pearson's product-moment correlations in cocaine users (n=38). Significant correlations are marked: *p<.05; **p<.01.
Means and standard deviations.
[a] Verbal IQ was assessed by the Mehrfachwahl Wortschatz Intelligenztest (Lehrl, 1999).
[b] ADHD-SR, ADHD self rating scale (cut-off DSM-IV criteria)(Roesler *et al*, 2004).
[c] Smoking habits were assessed by the Fagerstroem Test of Nicotine Dependence (Heatherton *et al*, 1991).
[d] BDI, Beck Depression Inventory (cut-off ≥18)(Hautzinger *et al*, 1994).
[e] Average use during the last 6 months.
[f] Craving for cocaine was assessed by the Brief-CCQ (Sussner *et al*, 2006).
[g] Cut-off values for cocaine = 150 ng/ml and for tetrahydrocannabinol = 50 ng/ml (Substance Abuse and Mental Health Services Administration, 2008).
[h] Parameters at follow-up refer to the 1-year period between t1 and t2.
[i] Last consumption is averaged only for persons who used the drug in the last 6 months.
[k] Use frequency, duration of use, and cumulative doses are averaged within the total group.

Table S2. Correlations between self reported cocaine use parameters and the hair toxicology parameter $cocaine_{total}$.

	Cocaine Users (n=38)	Cocaine Increasers (n=19)	Cocaine Decreasers (n=19)
Cocaine self-report at baseline	$Cocaine_{total}$ [a]	$Cocaine_{total}$	$Cocaine_{total}$
Times per week	.18	*.48	-.16
Grams per week	-.04	.12	-.18
Years of use	*.38	.39	.35
Max. dose (grams/day)	*.39	-.06	**.67
Cumulative dose lifetime (grams)	**.48	.22	**.62
Cocaine self-report at 1-year follow-up	$Cocaine_{total}$ [a]	$Cocaine_{total}$	$Cocaine_{total}$
Times per week	.14	-.05	.03
Grams per week	.08	-.04	.16
Years of use	.07	.12	.28
Max. dose (grams/day)	.29	.40	.06
Cumulative dose in the last year (grams)	.02	-.06	-.01

Pearson's product-moment correlations in cocaine users (n=38). Significant correlations are marked: *p<.05; **p<.01.
Cocaine parameters at 1-year follow-up refer to the period between t1 and t2.
[a] $Cocaine_{total}$ = Cocaine + Benzoylecgonine + Norcocaine.

Table S3. Cognitive test scores at the baseline (t1) and the 1-year follow-up (t2).

	Baseline (t1)							1-year follow-up (t2)						
	Controls (n=48)	Cocaine Increaser (n=19)	Cocaine Decreaser (n=19)	F[a]	df, df_{err}	p	Part. Eta^2	Controls (n=48)	Cocaine Increaser (n=19)	Cocaine Decreaser (n=19)	F[a]	df, df_{err}	p	Part. Eta^2
Attention														
RVP Discrimination perf. A'	0.92 (0.04)	0.90 (0.04)	0.90 (0.04)	1.92	2,83	.15	.04	0.93 (0.04)	0.91 (0.04)	0.92 (0.04)	2.00	2,83	.14	.05
RVP Total hits	18.35 (4.21)	16.26 (4.62)	16.79 (4.38)	1.95	2,83	.15	.04	19.98 (4.19)	17.79 (4.77)	18.63 (3.85)	2.02	2,83	.14	.05
RAVLT Supraspan trial 1[b]	9.38 (2.47)	8.47 (2.2)	8.26 (2.18)	1.99	2,82	.14	.05	9.66 (2.43)	8.68 (2.08)	9.37 (2.87)	1.06	2,82	.35	.03
Working memory														
LNST Score	15.54 (2.92)	14.00 (3.48)	14.00 (2.56)	2.84	2,83	.06	.06	15.69 (3.10)	13.74 (3.11)	14.32 (2.94)	3.27	2,83	**.04**	.07
SWM Total errors	20.31 (16.38)	27.11 (19.75)	26.95 (19.77)	1.49	2,83	.23	.03	13.52 (14.14)	25.53 (15.99)*	20.84 (15.64)	4.94	2,83	**.009**	.11
PAL First trial memory score	15.48 (3.87)	13.84 (4.26)	13.58 (2.43)	2.45	2,83	.09	.06	16.42 (3.08)	13.95 (3.63)*	15.63 (3.70)	3.71	2,83	**.03**	.08
Declarative memory														
RAVLT Learning perf. (∑trials 1-5)[b]	63.38 (6.53)	57.37 (9.66)*	57.84 (10.30)*	5.19	2,82	**.008**	.11	64.40 (6.64)	58.26 (10.55)*	62 (10.00)	3.63	2,82	**.03**	.08
RAVLT Adjusted recognition p(A)[b]	0.87 (0.11)	0.84 (0.19)	0.85 (0.14)	.54	2,82	.59	.01	0.87 (0.11)	0.84 (0.16)	0.86 (0.18)	.31	2,82	.73	.01
RAVLT Delayed recall trial 7[b]	13.19 (2.00)	12.00 (3.04)	11.89 (2.92)	2.66	2,82	.08	.06	13.66 (1.77)	12.05 (3.66)	13.42 (2.39)	3.00	2,82	.06	.07
PAL Total errors adjusted	11.96 (13.76)	19.32 (15.73)	15.00 (12.11)	1.95	2,83	.15	.04	6.96 (6.69)	18.47 (16.17)**	11.74 (17.59)	6.17	2,83	**.003**	.13
PAL Total trials adjusted	8.71 (3.44)	10.74 (4.01)	9.63 (3.29)	2.31	2,83	.11	.05	7.88 (2.20)	10.37 (4.09)**	8.47 (3.61)	4.62	2,83	**.01**	.10
Executive functions														
SWM Strategy score	32.27 (6.13)	33.53 (6.28)	33.00 (5.45)	.32	2,83	.72	.01	29.54 (6.03)	31.47 (6.81)	32.89 (4.41)	2.40	2,83	.10	.05
RAVLT Recall consistency (%)	93.05 (5.75)	87.54 (9.84)*	87.70 (8.61)*	5.52	2,82	**.006**	.12	93.43 (6.34)	88.76 (10.97)	91.61 (6.06)	2.61	2,82	.08	.06

Means and standard deviations. Significant p values are shown in bold.
[a] ANOVA (all groups, with significant Sidak post-hoc test vs. control group: *p<.05; **p<.01; ***p<.001).
[b] In the RAVLT task, the value for one control subject is missing due to a technical failure.

Table S4. Test-retest effect adjusted and ADHD corrected cognitive change scores between baseline (t1) and one-year follow-up (t2).

Change scores (Δ_{t2-t1})	Cocaine Increasers (n=19)	Cocaine Decreasers (n=19)
Global Cognitive Index	-0.09 (0.10)	0.15 (0.10)
Neurocognitive domains		
Attention	-0.02 (0.15)	0.16 (0.15)
Working memory	-0.22 (0.10)	0.10 (0.10)
Declarative memory	-0.14 (0.18)	0.23 (0.18)
Executive functions	0.02 (0.17)	0.11 (0.17)
Attention		
RVP Discrimination perf. A'	0.00 (0.01)	0.00 (0.01)
RVP Total hits	-0.10 (0.78)	0.22 (0.78)
RAVLT Supraspan trial 1	-0.10 (0.55)	0.86 (0.55)
Working memory		
LNST Score	-0.40 (0.64)	0.16 (0.64)
SWM Total errors	5.14 (2.99)	0.76 (2.99)
PAL First trial memory score	-0.83 (0.82)	1.12 (0.82)
Declarative memory		
RAVLT Learning perf. (∑trials 1-5)	-0.24 (1.79)	3.25 (1.79)
RAVLT Adjusted recognition p(A)	0.01 (0.04)	0.02 (0.04)
RAVLT Delayed recall trial 7	-0.44 (0.53)	1.08 (0.53)
PAL Total errors adjusted	4.25 (2.64)	1.65 (2.64)
PAL Total trials adjusted	0.49 (0.66)	-0.35 (0.66)
Executive functions		
SWM Strategy score	0.66 (0.96)	2.64 (0.96)
RAVLT Recall consistency in %	0.73 (1.58)	3.64 (1.58)

Mean change scores and standard errors (values corrected for ADHD). Change scores are adjusted for the test-retest effect.

Table S5. Correlations between cognitive change scores and cocaine use parameters during the interval period.

Change scores (Δ_{t2-t1})	Cocaine use during the interval period (between baseline and 1-year follow-up)	
	Cumulative dose (grams)	Hair analysis $Cocaine_{total}$ ng/mg
Attention		
RVP Discrimination perf. A'	*.36	
RVP Total hits	*.34	
RAVLT Supraspan trial 1		
Declarative memory		
RAVLT Learning perf. (∑trials 1-5)	.31	
RAVLT Adjusted recognition p(A)		*-.39
RAVLT Delayed recall trial 7	**.44	-.28
PAL Total errors adjusted		
PAL Total trials adjusted		

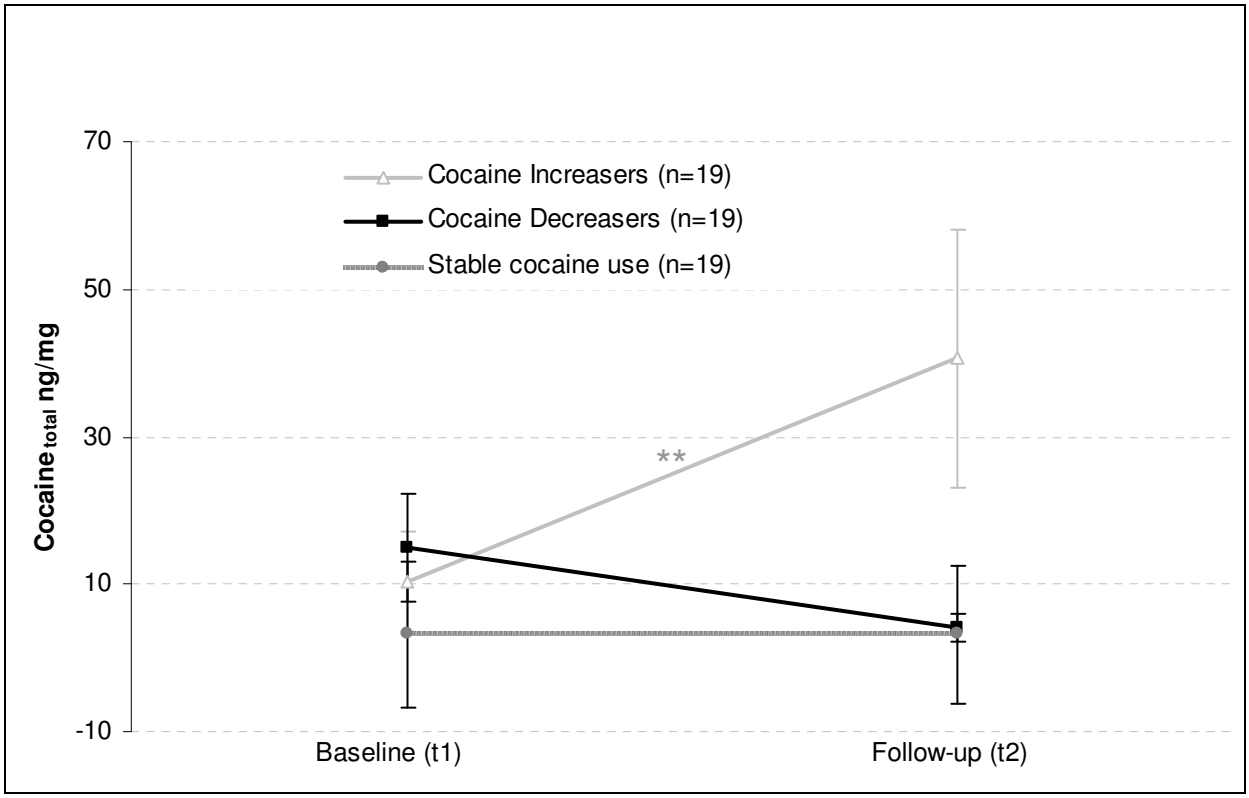
Pearson's product-moment correlations in cocaine users (n=35).
Correlations with a p-level below 10% (2-tailed) are shown, while significant correlations are marked: *p<.05; **p<.01.
Three cocaine users with more than 4 standard deviations difference in cumulative doses or $cocaine_{total}$ were excluded.

Table S6. Demographic data and hair analysis in cocaine user subgroups.

	Controls (n=48)	Cocaine Increasers low, <10 ng/mg (n=11)	Cocaine Increasers high, >10 ng/mg (n=8)	Cocaine Decreasers ongoing use (n=11)	Cocaine Decreasers no more use (n=8)	F	df, df_{err}	p
Global Cognitive Index (Δ_{t2-t1})[d]	0.00 (0.38)	-0.04 (0.48)	-0.15 (0.42)	0.04 (0.51)	0.29 (0.34)	1.3[a]	4,81	.28
Demographic data								
Age, y	30.3 (8.9)	29.5 (8.5)	34.3 (10.4)	33.5 (9.3)	28.5 (6.0)	.80[a]	4,81	.53
Sex (f/m)	16/32	3/8	0/8	3/8	2/6	3.84[b]	4	.43
Verbal IQ (MWT-B)	107.6 (10.0)	104.1 (12.1)	101.3 (5.5)	102.6 (8.5)	105.4 (4.7)	1.28[a]	4,81	.28
Education, y	10.8 (1.8)	10.7 (2.0)	10.0 (1.6)	10.3 (1.8)	9.6 (1.1)	.99[a]	4,81	.42
Smoking (y/n)	37/11	9/2	5/3	8/3	6/2	1.08[b]	4	.90
BDI score (0-63)	3.5 (3.3)	7 (4.5)	7.8 (11.5)	8.5 (7.9)	9.0 (4.6)	3.72[a]	4,81	**.008**
ADHD-SR score (0-22)	7.7 (5.2)	12.5 (9.4)	14.9 (9.8)	13.3 (6.7)	15.1 (7.3)*	4.60[a]	4,81	**.002**
Weeks between t1 and t2	58.2 (10.1)	58.4 (11.0)	60.6 (14.2)	62.4 (13.9)	61.2 (16.4)	.39[a]	4,81	.81
Hair analysis cocaine$_{total}$ ng/mg								
t1	-	2.9 (3.0)	20.3 (44.6)	23.8 (40.7)	2.6 (2.6)	1.37[c]	3,34	.27
t2	-	5.8 (3.4)°°	88.7 (101.6)	7.2 (9.9)°°	0.1 (0.2)°°	6.90[c]	3,34	**<.001**
Δ_{t2-t1}	-	+2.9 (2.4)°	+68.3 (83.8)	-16.6 (34.5)°°°	-2.5 (2. 6)°	6.82 [c]	3,34	**.001**

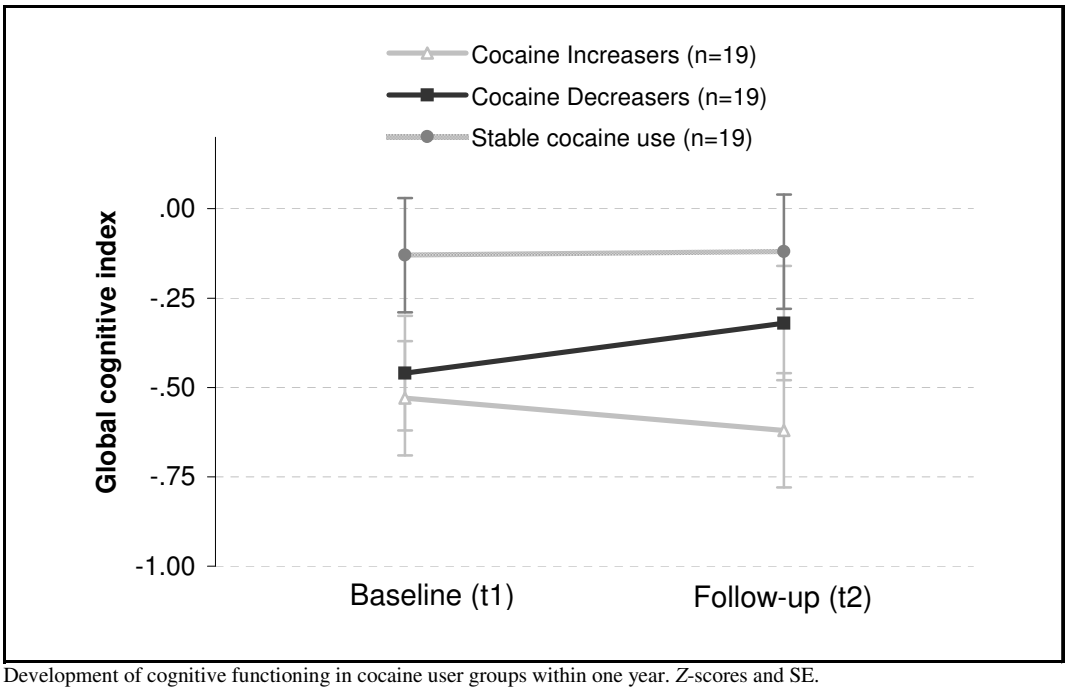
[a] ANOVA (all groups, with significant Sidak post-hoc test vs. control group:*p<.05).
[b] χ^2 test (all groups) for frequency data.
[c] ANOVA (only cocaine user groups, with significant Sidak post-hoc test vs. subgroup cocaine increaser high: °p<.05; °°p<.01; °°°p<.001).
[d] GCI change scores are adjusted for the test-retest effect.

Figure S1. Hair concentration cocaine$_{total}$ in three cocaine user groups at baseline (t1) and one-year follow-up (t2).



Hair concentration cocaine$_{total}$ (ng/mg) in cocaine user groups. Means and standard deviation. A mixed design analysis (ANOVA) showed a significant group*test interaction effect ($F_{2,54}$=5.70, p<.10). **indicates a significant pairwise Sidak pre-post comparison (p<.10).

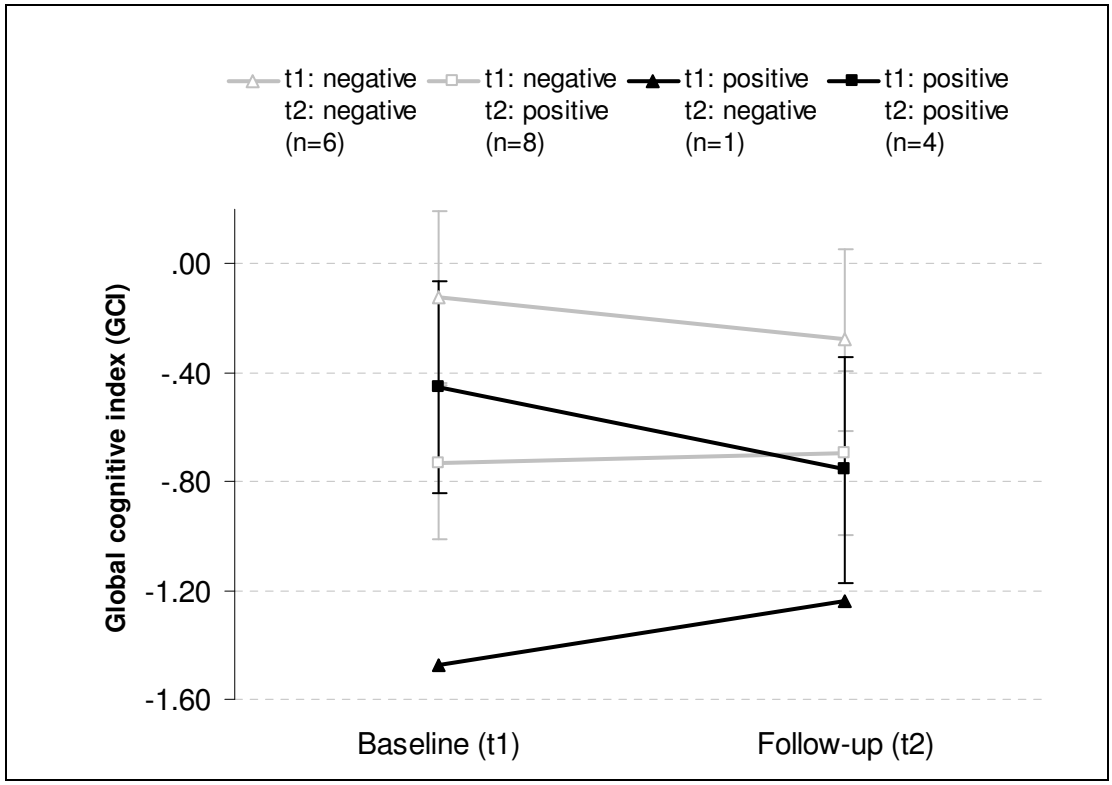
Figure S2. Development of cognitive functioning in all three cocaine user groups within one year.



Development of cognitive functioning in cocaine user groups within one year. *Z*-scores and SE.
Z-score transformation was based on control group mean and standard deviation at baseline. Values at follow-up were adjusted for the test-retest effect.
A mixed design analysis (corrected for ADHD) showed a non-significant group*time interaction effect ($F_{2,53}$=1.22, p=.30).
Pairwise Sidak pre-post comparisons were non-significant for *increasers* (p=.41), *decreasers* (p=.18), and *stable* cocaine users (p=.89).

As presented in Figure S1 (or more detailed in Table 1 and Table S1), the user group with *stable* cocaine use consists mainly of subjects with a comparatively low level of current cocaine use, whereas the *increaser* and *decreaser* groups consist of subjects with a substantially stronger former and/or current drug use. Consequently, GCI scores of the *stable* cocaine users are on a higher level than the GCI scores of the two other user groups.

Figure S3. Impact of cocaine urine toxicology status on global cognitive performance in cocaine *increasers* at baseline (t1) and 1-year follow-up (t2).



Development of cognitive functioning in cocaine user groups within one year. Z-scores and standard errors in groups stratified for urine toxicology (negative/positive) at baseline and follow-up in cocaine *increasers* (*n*=19).
Z-score transformation was based on control group mean and standard deviation at baseline. Values at follow-up were adjusted for the test-retest effect.
A mixed design analysis (corrected for ADHD) showed a non-significant group*time interaction effect ($F_{3,14}$=0.75, *p*=.54).
All pairwise Sidak pre-post comparisons were non-significant.

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